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HEPATOBILIARY DISEASE

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Background: Diets with a high glycaemic response exacerbate the metabolic consequences of the insulin resistance syndrome. Their effects on the incidence of gall stone disease are not clear, particularly in men.
Methods: Dietary information was collected as part of the Health Professionals Follow up Study starting in 1986 using a semiquantitative food frequency questionnaire with follow up until 1998. On biennial questionnaires participants reported new symptomatic gall stone disease, diagnosed by radiology, and whether they had undergone cholecystectomy.
Results: During 12 years of follow up, we documented 1810 new cases of symptomatic gall stones. After adjusting for age and other known or suspected risk factors in multivariate models, the relative risk (RR) for the highest compared with the lowest quintile of carbohydrate intake was 1.59 (95% confidence interval (CI) 1.25, 2.02; p for trend = 0.002). The RR for the highest compared with the lowest quintile of dietary glycaemic load was 1.50 (95% CI 1.20, 1.88; p for trend = 0.0008), and 1.18 for dietary glycaemic index (95% CI 1.01, 1.39; p for trend = 0.04). Independent positive associations were also seen for intakes of starch, sucrose, and fructose.
Conclusions: Our findings suggest that a high intake of carbohydrate, glycaemic load, and glycaemic index increases the risk of symptomatic gall stone disease in men. These results add to the concern that low fat high carbohydrate diets may not be an optimal dietary recommendation.

Gall stone disease is a common abdominal condition affecting adults in Western populations,[1] and is a leading cause of digestive related hospital admissions.[1–3] Therefore, preventive measures to decrease the occurrence of gall stone disease are required.

Many factors have been associated with the risk of cholesterol gall stones but supersaturation of bile with cholesterol is an important determinant.[4] Low plasma high density lipoprotein (HDL) cholesterol and high plasma triglyceride levels were found to be associated with a greater risk of gall stone disease.[5] High intake of carbohydrates raises plasma fasting triglyceride, primarily by enhancing hepatic synthesis of very low density lipoprotein (VLDL) cholesterol, and can also reduce HDL cholesterol[6 7] and thus may increase the risk of gall stones. Carbohydrates with different physical forms, chemical structures, particle sizes, and fibre contents may induce distinct plasma glucose and insulin responses. The physiological response to carbohydrates can be quantified by glycaemic index.[8] Substituting foods with low glycaemic indices for those with high indices may reduce serum insulin and glucose response in diabetics and healthy subjects,[9 10] although the results have not been entirely consistent.[11] Also, a chronic high dietary glycaemic load, which increases insulin demand, may exacerbate insulin resistance[12 13] and hence may increase the risk of gall stone disease.[14 15]

Epidemiological studies of carbohydrate consumption and gall stone disease have shown mixed results.[16–20] Although the available evidence indicates that insulin resistance, chronic hyperglycaemia, and associated disorders of lipid metabolism are important predictors of gall stone disease, the relationship between dietary glycaemic load and glycaemic index and the risk of gall stone disease have not been examined.

In a large cohort of US male health professionals, we examined the relation between a high carbohydrate intake and the risk of symptomatic gall stones. Furthermore, we examined if diets characterised by high glycaemic load or high glycaemic index would increase the risk of symptomatic gall stone disease.

METHODS

Study population

The Health Professionals Follow up Study is a prospective investigation of 51 529 US male health professionals, aged 40–75 years in 1986, who returned a mailed questionnaire regarding diet, medications, and medical history. The study population included 29 683 dentists, 10 098 veterinarians, 4185 pharmacists, 3745 optometrists, 2218 osteopathic physicians, and 1600 podiatrists. Participants in this cohort were mainly Caucasian (>91%). Follow up questionnaires were sent every two years to update information on exposures and to ascertain the occurrence of newly diagnosed illnesses, including gall stone disease. Diet was assessed in 1986, 1990, and 1994. At baseline, we excluded men who reported a cholecystectomy or a diagnosis of gall stone disease before 1986. Also, we excluded men who had a diagnosis of cancer before 1986, men who had a daily energy intake outside the range of 800–4200 kcal/day, and men who reported 70 or more blank food items on the questionnaires. We further excluded participants with a diagnosis of diabetes mellitus because diabetes could be an intermediary in the causal pathway between exposures and outcome. After exclusions, the study population consisted of 44 525 eligible men who were followed from 1986 to 1998. The average response rate for biennial questionnaires was greater than 94% in each two year follow up cycle.[21] The remaining non-responding participants were assumed to be alive if not listed in the National Death Index.

Abbreviations: HDL, high density lipoprotein; VLDL, very low density lipoprotein; SFFQ, semiquantitative food frequency questionnaire

Assessment of diet

Dietary information was derived from a 131 item semiquantitative food frequency questionnaire (SFFQ).[22] Participants were asked to indicate the frequency, on average, of consuming a typical serving of selected foods during the previous year. There were nine possible response options, ranging from never or less than once per month to six or more times per day. Nutrient scores were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion according to food composition tables from the US Department of Agriculture.[23]

For each participant, we derived an average dietary glycaemic index value which ranks foods on the basis of the incremental glucose response and insulin demand for a given amount of carbohydrate.[24] We calculated the average dietary glycaemic index by summing the products of the carbohydrate content per serving for each food multiplied by the average number of servings of that food per day, times its glycaemic index, and all divided by the total amount of daily carbohydrate intake.[25] For these calculations, we used published data for the carbohydrate content in each serving reported by the US Department of Agriculture.[23 25] We also calculated glycaemic load by multiplying the carbohydrate content of each food by its glycaemic index, then multiplied this value by the frequency of consumption, and summed up the values from all foods.[26] Dietary glycaemic load represents the quality and quantity of carbohydrates and the interaction between the two, and also indicates the glucose response and insulin demand induced by total carbohydrate intake. Each unit of dietary glycaemic load represents the equivalent of 1 g of carbohydrate from pure glucose.

The validity and reproducibility of the SFFQ was assessed in a random sample of 127 participants living in the Boston, Massachusetts, area.[22] We compared nutrient intakes from the SFFQ with two detailed one week diet records spaced approximately six months apart, on which all foods consumed each day were recorded. A full description of the SFFQ and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity in this cohort, were reported previously.[27] All nutrients, as well as glycaemic index and glycaemic load, were adjusted for total energy intake using regression analysis. This approach is based on the concept that the composition of the diet, independent of total energy intake, is most relevant to dietary recommendations.[27]

Ascertainment of end points

The primary end point was incident symptomatic gall stones. In 1986 and on each follow up questionnaire, participants were asked whether they had undergone a cholecystectomy or had been diagnosed as having gall stones by a physician. Participants were also asked whether the gall stone diagnosis had been confirmed by radiographic procedures or surgery and whether their gall stones were symptomatic. To verify the self reports of surgical cholecystectomy and diagnosed but unremoved gall stones, a random sample of 441 medical records of participants who reported a cholecystectomy or gall stones were reviewed and the diagnosis was confirmed in nearly all (99%) of these cases. Moreover, we confirmed all but one of the self reported diagnostic procedures and all self reported symptoms by medical record review. Although the composition of the gall stones was not assessed, it was estimated that approximately 80% of gall stones in the study population were cholesterol stones.[28]

Statistical analysis

For each participant, follow up time accrued from the month of return of the 1986 questionnaire and ended at the month of cholecystectomy, diagnosis of symptomatic gall stones, death, or the end of the study period on 31 January 1998, whichever occurred first. Men with asymptomatic gall stones or those whose gall stone diagnosis was not based on radiology, and men with diagnosed cancer or diabetes mellitus were excluded from subsequent follow up. Thu, the eligible population at risk comprised only those who remained free of symptomatic gall stone disease, cancer, and diabetes mellitus at the beginning of each two year follow up interval.

Men were grouped in quintiles of carbohydrate intake, dietary glycaemic load, and overall dietary glycaemic index. Incidence rates were calculated by dividing the number of events by person years of follow up in each quintile. Relative risks were calculated as the incidence rate of symptomatic gall stone disease among men in different categories of exposure compared with the incidence rate among men in the reference category, with adjustment for age in five year categories. Age adjusted relative risks were calculated using the Mantel-Haenszel summary estimator.[29] For multivariate analyses, the estimated relative risks for gall stone disease were simultaneously adjusted for potential confounding variables using a pooled logistic regression model with two year time increments. The pooled logistic regression model is a generalised person years approach originally used in the Framingham Heart Study data, in which risk factors were measured every two years with a follow up between these measurement times to observe the occurrence of events. Observations over multiple intervals are pooled into a single sample and a logistic regression is employed to relate the risk factors to the occurrence of the event.[30 31] In this study, relative risk is equivalent to the incidence rate ratio, given the low incidence of symptomatic gall stones in this large study population within each follow up period. This method accounts for varying time to the outcome event and is asymptotically equivalent to Cox regression with time dependent covariates.[31]

Tests for linear trends were computed using continuous variables in the models. The incidence of symptomatic gall stone disease was examined in relation to the cumulative average of exposure variables from all available questionnaires up to the start of each two year follow up interval, using methods for repeated measurement.[32] We cumulatively updated carbohydrate intake in 1990 and 1994 to provide a better estimate of the effect of long term average carbohydrate consumption. Specifically, the average intake reported on the 1986 questionnaire was related to the incidence of symptomatic gall stone disease from 1986 to 1990, average intake reported on the 1986 and 1990 questionnaires was related to the incidence from 1990 to 1994, and average intake reported on the 1986, 1990, and 1994 questionnaires was related to the incidence from 1994 to 1996.

In multivariate analyses, we simultaneously included intake of total energy and potential confounding covariates, including biennially updated age (five year categories), body mass index (calculated as weight in kilograms divided by the square of height in meters) (five categories), weight change during the past two years (five categories), dietary fibre (quintiles), protein intake (quintiles), pack years of smoking (six categories), physical activity (quintiles), intakes of caffeine (quintiles) and alcohol (five categories), thiazide diuretics (yes or no), and non-steroidal anti-inflammatory drugs (yes or no). In the subgroup analyses for potential effect modification, median values of intakes of alcohol and caffeine, age, body mass index, and physical activity were used as the cut off points. All relative risks are presented with 95% confidence interval (CI), and all reported p values are two sided. All analyses were performed using the Statistical Analysis System software, release 6.12 (SAS Institute, Cary, North Carolina, USA).

Table 1 Baseline characteristics according to quintiles of energy adjusted carbohydrate intake in 44 525 US men in 1986: the Health Professionals Follow up Study

Characteristic	Quintiles of carbohydrate intake				
	1 (lowest)	2	3	4	5 (highest)
Participants (n)	8869	8883	8940	8947	8886
Quintile mean intake (g/day)	176.6	213.0	234.2	255.8	295.2
Body mass index (kg/m^2)	25.4 (5.1)	25.2 (5.1)	24.9 (4.8)	24.5 (4.8)	24.2 (4.6)
Physical activity (METs)*	16.5 (20.7)	18.4 (23.6)	20.1 (24.8)	21.1 (26.6)	24.6 (28.9)
Total energy (kcal/day)	1962 (631)	2025 (611)	2031 (621)	1992 (607)	1943 (617)
Protein (g/day)	99.4 (19.0)	95.3 (15.0)	92.6 (14.2)	89.5 (13.9)	83.6 (14.9)
Alcohol (g/day)	22.8 (22.0)	13.6 (15.3)	9.7 (11.7)	7.0 (9.2)	4.6 (7.2)
Caffeine (mg/day)	311 (284)	266 (253)	243 (244)	218 (236)	175 (220)
Cholesterol (mg/day)	373 (133)	331 (96)	305 (87)	276 (75)	221 (75)
Saturated fat (g/day)	28.8 (6.4)	26.8 (5.1)	25.0 (4.5)	22.9 (4.3)	18.5 (4.8)
Polyunsaturated fat (g/day)	14.4 (4.3)	13.9 (3.3)	13.5 (3.0)	12.8 (2.8)	11.4 (3.0)
Monounsaturated fat (g/day)	32.0 (6.1)	29.7 (4.6)	27.8 (4.1)	25.6 (3.9)	20.9 (4.6)
Trans fat (g/day)	3.0 (1.1)	3.1 (1.1)	3.0 (1.1)	2.8 (1.1)	2.2 (1.1)
Dietary fibre (g/day)	16.1 (4.4)	18.8 (4.6)	20.5 (5.0)	22.3 (5.7)	27.0 (9.2)
Current smoker (%)	16.3	11.3	8.1	6.5	4.4

Values are mean (SD).
*METs, metabolic equivalent tasks per week, defined as a multiple of metabolic equivalent of sitting at rest.

RESULTS

At baseline in 1986 there was an approximately 1.5-fold difference in the mean energy-adjusted carbohydrate intake between the highest and lowest quintiles at baseline (table 1). Men with higher carbohydrate intake consumed less protein and saturated, *trans*, monounsaturated, and polyunsaturated fats. Men who reported higher intake of carbohydrate tended to be leaner, more physically active, non-smokers, consume less alcohol and caffeine, but more dietary fibre.

During 457 699 person years of follow up from 1986 to 1998, we ascertained 1810 cases of symptomatic gall stones, of which 1025 had undergone cholecystectomy. After adjustment for age, the estimated relative risk for men in the highest quintile compared with those in the lowest quintile of energy adjusted dietary glycaemic load was 1.28 (95% CI 1.10, 1.49; p for trend = 0.02) (tables 2, 3). This association was slightly strengthened after further adjustment for other known or suspected risk factors for gall stones. In an analysis that included age, body mass index, weight change during the past two years, physical activity, thiazide diuretics, non-steroid anti-inflammatory drugs, pack years of smoking, alcohol, caffeine, dietary fibre, protein, *trans* fat, saturated fat, and total energy intake (model 3; tables 2, 3), the relative risk for the highest compared with the lowest quintile of dietary glycaemic load was 1.50 (95% CI 1.20, 1.88; p for trend = 0.0008).

We further adjusted for intakes of all fats (model 4; tables 2, 3). In this model, in which all fats, protein, and total energy intake were held constant, glycaemic load represents the effect of substituting high glycaemic index carbohydrates for low glycaemic index carbohydrates on the risk of symptomatic gall stone disease. Compared with carbohydrates with a low glycaemic index, carbohydrates with a high glycaemic index were associated with an increased risk. The relative risk for the highest compared with the lowest quintile of glycaemic load was 1.46 (95% CI 1.14, 1.87; p for trend = 0.007).

The quality of carbohydrate, as classified by its glycaemic index, was also associated with the risk of symptomatic gall stone disease. After adjustment for age, the relative risk for men in the highest quintile compared with those in the lowest quintile of energy adjusted dietary glycaemic index was 1.26 (95% CI 1.08, 1.46; p for trend = 0.02) (tables 2, 3). In a multivariate analysis that included the same covariates as those for glycaemic load (model 3), the relative risk for the highest compared with the lowest quintile of dietary glycaemic index was 1.18 (95% CI 1.01, 1.39; p for trend = 0.04). Addition of types of fats to this model did not appreciably change the positive association between overall dietary glycaemic index and the risk of symptomatic gall stone disease.

Intake of total carbohydrate was significantly associated with an increased risk. In the multivariate model, the relative risk for the highest compared with the lowest quintile of dietary carbohydrate was 1.59 (95% CI 1.25, 2.02; p for trend = 0.002) (table 4). Carbohydrates have been classified as complex (polysaccharides, mainly starch) or simple

Table 2 Adjusted relative risks (95% confidence interval) of symptomatic gall stone disease according to quintiles of energy adjusted intakes of glycaemic load among US men in the Health Professionals Follow up Study, 1986–1998

	Quintiles of glycaemic load					
	1 (lowest)	2	3	4	5 (highest)	p for trend
Cases of GSD*	293	352	432	353	380	–
Person years	90 275	91 836	91 426	92 589	91 572	–
Model 1: age adjusted	1.00	1.09 (0.93, 1.28)	1.36 (1.17, 1.58)	1.24 (1.06, 1.44)	1.28 (1.10, 1.49)	0.02
Model 2: multivariate	1.00	1.09 (0.92, 1.29)	1.37 (1.16, 1.62)	1.25 (1.04, 1.50)	1.30 (1.07, 1.59)	0.03
Model 3: multivariate	1.00	1.13 (0.95, 1.33)	1.46 (1.23, 1.74)	1.38 (1.13, 1.67)	1.50 (1.20, 1.88)	0.0008
Model 4: multivariate	1.00	1.13 (0.95, 1.34)	1.46 (1.22, 1.75)	1.36 (1.10, 1.67)	1.46 (1.14, 1.87)	0.007

GSD, gall stone disease.
†Model 2, multivariate model included the following: age, body mass index, weight change during the past two years, physical activity, thiazide diuretics, non-steroid anti-inflammatory drugs, pack years of smoking, alcohol intake, caffeine intake, dietary fibre, protein intake, and total energy intake.
Model 3, model 2 with additional adjustment for saturated and *trans* fats.
Model 4, model 2 with additional adjustment for monounsaturated fat, polyunsaturated fat, saturated fat, and *trans* fat.

Table 3 Adjusted relative risks (95% confidence interval) of symptomatic gall stone disease according to quintiles of energy adjusted intakes of glycaemic index among US men in the Health Professionals Follow up Study, 1986–1998

	Quintiles of glycaemic index					
	1 (lowest)	2	3	4	5 (highest)	p for trend
Cases of GSD	359	319	356	388	388	–
Person years	90 354	92 143	91 537	92 142	91 522	–
Model 1: age adjusted	1.00	1.05 (0.90, 1.22)	1.16 (1.00, 1.34)	1.18 (1.02, 1.37)	1.26 (1.08, 1.46)	0.02
Model 2: multivariate	1.00	1.02 (0.88, 1.19)	1.11 (0.96, 1.29)	1.13 (0.97, 1.31)	1.16 (0.99, 1.35)	0.09
Model 3: multivariate	1.00	1.03 (0.88, 1.20)	1.12 (0.96, 1.30)	1.14 (0.98, 1.33)	1.18 (1.01, 1.39)	0.04
Model 4: multivariate	1.00	1.02 (0.88, 1.19)	1.12 (0.96, 1.30)	1.14 (0.97, 1.33)	1.17 (1.00, 1.38)	0.07

GSD, gall stone disease.
†Model 2, multivariate model included the following: age, body mass index, weight change during the past two years, physical activity, thiazide diuretics, non-steroid anti-inflammatory drugs, pack years of smoking, alcohol intake, caffeine intake, dietary fibre, protein intake, and total energy intake.
Model 3, model 2 with additional adjustment for saturated and *trans* fats.
Model 4, model 2 with additional adjustment for monounsaturated fat, polyunsaturated fat, saturated fat, and *trans* fat.

(monosaccharides and disaccharides). We therefore examined the relation of these mutually exclusive types of carbohydrate to the risk of symptomatic gall stone disease. In the multivariate models, we found that starch, sucrose, and fructose each had a significant positive relationship with the risk, while lactose did not (table 5).

To examine whether the association with carbohydrate intake was modified by other risk factors for gall stones, we repeated the multivariate analyses within subgroups of potential confounding variables (table 6). We found no apparent effect modification. The positive associations between carbohydrate intake and the risk persisted in all subgroups, although they were not always statistically significant, which would in part be due to the reduced sample sizes in the subgroups.

To evaluate the potential for detection bias due to increased medical surveillance among men with greater carbohydrate intake, we additionally excluded men with a routine medical check up between 1986 and 1988. Compared with men in the lowest quintile of carbohydrate intake, men in the highest quintile of carbohydrate had a multivariate relative risk of 1.97 (95% CI 1.39, 2.78; p for trend = 0.001).

We further addressed the possibility of detection bias by limiting the analysis to cholecystectomy cases. The multivariate relative risk for men in the highest quintile of carbohydrate intake compared with men in the lowest quintile (relative risk = 1.46; 95% CI 1.06, 2.00; p for trend = 0.11) was essentially unchanged although the confidence interval was wider due to fewer end points.

DISCUSSION

In this 12 year prospective cohort study among men, we found that a high intake of carbohydrate was positively associated with the risk of symptomatic gall stone disease. A significant positive association was also found for dietary glycaemic load and glycaemic index.

Epidemiological studies of carbohydrate or sugar intake and risk of gall stone disease have not been consistent. In a cross sectional study of gall stone disease in Copenhagen, ascertained by ultrasonography, higher intake of refined sugar was not significantly associated with increased gall stone prevalence.[18] In a population based health survey in Mexican Americans, in which participants were questioned about any history of gall bladder disease, high level of sucrose intake was not significantly related to the risk of gall stone disease.[19] In two larger case control studies, one in Italy and the other in Australia, an increased risk with sugar intake was seen.[16 33] In a prospective cohort study in the Netherlands, a twofold greater risk of clinically diagnosed gall stones was found for the highest tertile of sugar intake relative to the lowest.[17] In a population study in Italy, a positive association was observed between high carbohydrate intake and an increased risk of gall stones diagnosed in an ultrasonographic survey.[20] The inconsistency among these studies may be due to lack of long term dietary information, imprecise or non-validated assessment of nutrients, suboptimal study design, small sample size, or different definitions of disease end points.

High intake of carbohydrate stimulates hepatic synthesis of VLDL cholesterol, raises plasma triglycerides, and reduces HDL cholesterol.[6 7] In a prospective, randomised, long term outpatient study in free living subjects lasting up to two years,[34] a diet with high carbohydrate and low fat content was associated with an increase in plasma triglyceride level and a reduction in HDL cholesterol level. Low plasma HDL cholesterol and high triglyceride were found to be associated with an increased risk of gall stone disease.[5 35] In addition, a low fat, high carbohydrate diet may increase the incidence of glucose intolerance, type 2 diabetes mellitus, hyperinsulinaemia, and insulin resistance, and thereby may facilitate gall stone formation.[14 15] In metabolic trials, low fat, high carbohydrate diets decreased insulin sensitivity in subjects.[36 37] In subjects who were prone to insulin resistance, these diets further worsened dyslipidaemia.[38] Moreover, diets with high glycaemic index and glycaemic load diets have been reported to increase postprandial glucose and insulin responses, derange lipid profiles, and decrease insulin sensitivity,[12 39 40] which may increase the risk of gall stones.

Table 4 Adjusted relative risks (95% confidence interval) of symptomatic gall stone disease according to quintiles of dietary intakes of energy adjusted total carbohydrate among US men in the Health Professionals Follow up Study, 1986–1998

	Quintiles of carbohydrate					
	1 (lowest)	2	3	4	5 (highest)	p for trend
Model 1: age adjusted	1.00	1.13 (0.97, 1.32)	1.29 (1.11, 1.50)	1.17 (1.01, 1.37)	1.28 (1.10, 1.48)	0.01
Model 2: multivariate	1.00	1.19 (1.01, 1.41)	1.41 (1.18, 1.69)	1.35 (1.10, 1.65)	1.59 (1.25, 2.02)	0.002

Model 1, relative risk adjusted for age.
Model 2, the multivariate model included the same covariates as in model 3 in tables 2, 3.

Table 5 Adjusted relative risks (95% confidence interval) of symptomatic gall stone disease according to quintiles of dietary intakes of different types of carbohydrate* among US men in the Health Professionals Follow up Study, 1986–1998

	Quintiles					
	1 (lowest)	2	3	4	5 (highest)	p for trend
Starch						
Model 1: age adjusted	1.00	1.17 (1.01, 1.36)	1.16 (1.00, 1.35)	1.12 (0.96, 1.31)	1.24 (1.07, 1.45)	0.03
Model 2: multivariate	1.00	1.19 (1.02, 1.39)	1.20 (1.02, 1.41)	1.20 (1.01, 1.42)	1.43 (1.20, 1.72)	0.0002
Sucrose						
Model 1: age adjusted	1.00	1.12 (0.96, 1.30)	1.18 (1.01, 1.38)	1.23 (1.06, 1.44)	1.39 (1.20, 1.61)	<0.0001
Model 2: multivariate	1.00	1.09 (0.92, 1.28)	1.14 (0.96, 1.35)	1.16 (0.98, 1.38)	1.28 (1.07, 1.54)	0.002
Fructose						
Model 1: age adjusted	1.00	1.09 (0.94, 1.27)	1.05 (0.90, 1.22)	1.04 (0.90, 1.21)	1.23 (1.06, 1.42)	0.05
Model 2: multivariate	1.00	1.12 (0.96, 1.31)	1.09 (0.92, 1.28)	1.09 (0.92, 1.30)	1.30 (1.08, 1.57)	0.04
Lactose						
Model 1: age adjusted	1.00	1.22 (1.05, 1.42)	1.22 (1.05, 1.42)	1.28 (1.10, 1.48)	1.13 (0.97, 1.32)	0.8
Model 2: multivariate	1.00	1.18 (1.01, 1.37)	1.19 (1.01, 1.38)	1.24 (1.06, 1.44)	1.10 (0.93, 1.29)	0.9

Model 1, relative risk adjusted for age.
Model 2, the multivariate model included the same covariates as in model 3 in tables 2, 3.
*Carbohydrates were classified by their chemical structure. All types of carbohydrate included simultaneously. Types of carbohydrate were mutually exclusive; fructose does not include contribution from sucrose.

Men with a high carbohydrate intake tended to have a generally healthy lifestyle (see table 1), which may protect against gall stone disease. Our detailed analyses took into account the differences in lifestyle, and these adjustments appeared to strengthen the associations. It indicated that the associations were independent of these known risk factors.

The prospective design of our study avoids the potential for differential recall of intake by gall stone cases and non-cases because all data on food were collected before the diagnosis of symptomatic gall stone disease. Also, consistently high follow up rates reduce the possibility that our results are biased by men lost to follow up in this cohort. Thus these potential biases would have been minimal.

The possibility of misclassification might be of concern because information on nutrient intake was collected by self report. Random within person variation could attenuate any true association of interest but the semiquantitative food frequency questionnaire was designed to minimise this error by assessing average long term dietary intake during the successive follow up periods. These repeated measurements took into account possible changes in diet with time, and reduced random variation in reporting. Although the total effects of carbohydrate intake may not be fully captured by the questionnaire, any measurement errors would be expected to be unrelated to the end points because of the prospective design. Thus any non-differential misclassification would most likely bias the relative risks toward null and weaken, rather than strengthen, any true relationship.

Our results were restricted to men with surgical cholecystectomy or diagnostically confirmed but unremoved symptomatic gall stones. The results may not be generalisable to the entire population with gall stones; however, the study focused on clinically relevant gall stone disease.

In this large study population it was not possible to perform diagnostic screening procedures for the presence of gall stones. It is likely that the positive correlations found are related to an increasing risk for the transition from asymptomatic to symptomatic gall stones. Because most gall

Table 6 Adjusted relative risks* of symptomatic gall stone disease, stratified by potential confounders, according to quintiles of carbohydrate intake

		Quintiles of carbohydrate intake					
Variables	No of cases	1 (lowest)	2	3	4	5 (highest)	p for trend
Alcohol intake†							
High	796	1.00	1.20 (0.97, 1.48)	1.43 (1.13, 1.80)	1.69 (1.31, 2.19)	1.65 (1.19, 2.28)	0.004
Low	1014	1.00	1.28 (0.97, 1.70)	1.54 (1.17, 2.04)	1.29 (0.96, 1.75)	1.70 (1.21, 2.37)	0.03
Caffeine intake†							
High	830	1.00	1.24 (0.99, 1.56)	1.36 (1.06, 1.75)	1.16 (0.87, 1.56)	1.45 (1.02, 2.05)	0.18
Low	980	1.00	1.11 (0.87, 1.42)	1.43 (1.10, 1.85)	1.47 (1.11, 1.96)	1.70 (1.22, 2.37)	0.003
Physical activity† (METs‡)							
High	765	1.00	1.09 (0.83, 1.42)	1.26 (0.95, 1.68)	1.18 (0.86, 1.62)	1.27 (0.88, 1.84)	0.25
Low	1037	1.00	1.26 (1.02, 1.56)	1.51 (1.19, 1.90)	1.45 (1.11, 1.89)	1.86 (1.36, 2.54)	0.003
Body mass index (kg/m^2)							
⩾25	1110	1.00	1.20 (0.98, 1.47)	1.41 (1.12, 1.76)	1.38 (1.07, 1.78)	1.66 (1.22, 2.25)	0.01
<25	656	1.00	1.18 (0.87, 1.60)	1.40 (1.02, 1.92)	1.22 (0.86, 1.73)	1.36 (0.91, 2.02)	0.20
Age (y)†							
⩾52	1301	1.00	1.19 (0.97, 1.46)	1.47 (1.19, 1.83)	1.44 (1.13, 1.83)	1.64 (1.24, 2.18)	0.002
<52	509	1.00	1.19 (0.88, 1.60)	1.30 (0.94, 1.81)	1.21 (0.83, 1.77)	1.65 (1.05, 2.59)	0.18
Weight change within past 2 y							
>4 lb	318	1.00	1.15 (0.78, 1.71)	1.72 (1.14, 2.61)	1.39 (0.86, 2.24)	1.61 (0.91, 2.86)	0.02
⩽4 lb	1041	1.00	1.22 (0.98, 1.52)	1.19 (0.93, 1.52)	1.27 (0.97, 1.66)	1.57 (1.15, 2.15)	0.04
Current smoking							
Yes	1013	1.00	1.23 (1.00, 1.52)	1.49 (1.18, 1.88)	1.38 (1.06, 1.80)	1.65 (1.20, 2.26)	0.02
No	797	1.00	1.10 (0.84, 1.46)	1.29 (0.96, 1.72)	1.27 (0.92, 1.74)	1.49 (1.04, 2.16)	0.04

*The multivariate model included the same covariates as in model 3 in tables 2, 3. The variable used for stratification was excluded from the model.
†Median values were used as cut off points.
‡ METs, metabolic equivalent tasks per week, defined as a multiple of metabolic equivalent of sitting at rest.

stones are silent, it is likely that there was considerable under ascertainment of gall stones. It was not likely that the presence of silent gall stones at baseline was associated with the reporting. As relative risk estimation in follow up cohort studies would not be biased by uniform under ascertainment,[29] our results were not likely biased due to silent gall stones.

In conclusion, our findings suggest that a high intake of carbohydrate, glycaemic load, and glycaemic index increases the risk of symptomatic gall stone disease among men. These results add to the concern that low fat, high carbohydrate diets may not be an optimal dietary recommendation.

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